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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/976,468	10/12/2001	Jorge DiMartino	12636-219	9964

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EXAMINER	
LEWIS, PATRICK T	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 09/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/976,468	DIMARTINO ET AL.	
	Examiner	Art Unit	
	Patrick T. Lewis	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45-54 and 56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45-54 and 56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group II in the reply filed on March 14, 2003 is acknowledged.

Applicant's Response Dated June 28, 2004

2. In the Response dated June 28, 2004, claims 45 and 56 were amended; claim 55 was canceled.

3. Claims 45-54 and 56 are pending. An action on the merits of claims 45-54 and 56 is contained herein below.

4. The rejection of claims 19, 21-22, 25-27 and 31-33 under 35 U.S.C. 112, first paragraph, has been rendered moot in view of applicant's amendment dated June 28, 2004.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. Claims 45-54 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Waller U.S. 5,800,539 (Waller) in combination with Trotta et al. *Cancer Research*, **1981**, Vol. 41, pages 2189-2196 (Trotta); and Spaner U.S. 6,258,357 (Spaner).

Claim 45 is drawn to a method for preventing or reducing the risk of developing graft-versus-host disease in a recipient of an organ or tissue transplant, comprising administering to the transplant recipient pentostatin in a pharmaceutically effective amount within a predetermined time window before the transplantation. Claims 46-54 and 56 depend from claim 45. Claims 46-48 limit the transplantation performed. Claims 49-54 limit the administration regimen of pentostatin. Claim 56 further requires the administration of an immunosuppressive agent.

Waller teaches a method of transplanting hematopoietic system reconstituting cells from a donor source into an allogeneic recipient comprising administering to the recipient, prior to the administration of the hematopoietic system reconstituting cells, an amount of mononuclear cells which are treat so as to render them incapable of proliferating and causing a lethal GVHD effect, but which are effective in enhancing subsequent engraftment of the hematopoietic system reconstituting cells in the recipient; and administering to the recipient an effective amount of hematoietic system reconstituting cells (column 3, lines 32-43). The mononuclear cells are treated with cytotoxic chemotherapeutic drugs to render the cells incapable of proliferating and causing GVHD (column 4, lines 66-67; column 5, line 1). Examples of cytotoxic chemotherapeutic drugs to be employed include but are not limited to mitomycin C, bleomycin, fludarabine, and doxirubicin (column 5, lines 1-15). The treated mononuclear cells are administered to the recipient at any time prior to the administration of the hematopoietic system reconstituting cells. Any range of treatment, e.g., one to nine, two to eight, three to seven, one to two, one to three, zero to one, zero to two days, etc. are also provided (column 5, lines 38-48). The amount of treated mononuclear cells administered to the recipient range between 0.05×10^6 and 30×10^6 mononuclear cells/kg of recipient's body weight (column 5, lines 57-61). The treated mononuclear cells and hematopoietic system reconstituting cells are typically administered to the recipient in a pharmaceutically acceptable carrier by intravenous infusion (column 7, lines 1-6).

Waller differs from the instantly claimed invention in that Waller: 1) does not teach oral administration, 2) does not teach the use of pentostatin, and 3) does not teach the co-administration of an immunosuppressive agent. The deficiencies of Waller however would have been obvious to one of ordinary skill in the art at the time of the invention in view of Trotta, and Spaner, collectively.

Trotta teaches the use of adenosine deaminase inhibitors in the prevention of graft-versus-host disease in hematopoietic transplantation (page 2189, ABSTRACT; page 2194, column 2, paragraphs 2-3). Trotta teaches that DCF (pentostatin) is infused continuously at a concentration of 0.8 mg/ml for a 20-g mouse (page 2190, column 1, paragraph 3). The effects of DCF administration also provide a theoretical basis for a new approach to the treatment of diseases of the lymphoreticular system by bone marrow transplantation. The usefulness of such transplantation has been limited by severe GVHD, which is invariably fatal unless donor and recipient are perfectly matched at the major histocompatibility locus. Treatment of lethally irradiated mice with fetal liver or newborn spleen cells supports the concept that graft-versus-host reactions might not ensue if postthymic T-cells were absent from the reconstituting tissue. The results imply that elimination of differentiated lymphoid cells from the engrafting stem cell population would allow bone marrow transplantation using cells from unrelated individuals. In addition to the treatment of diseases of hematopoietic and immunological function, such an approach might have additional application in the achievement of organ transplantation without immunological rejection. In light of the specific lymphocytotoxicity of DCF *in vivo*, either *in vivo* pretreatment of the donor or *in vitro*

treatment of the graft with an Adase inhibitor might be selective in destroying postthymic T-cells. This result contrasts with the toxicity of current immunosuppressives to tissues outside of the lymphoid system, including bone marrow. The use of DCF to promote transplantation across major histocompatibility barriers is thus a reasonable hypothesis based on these data.

Spaner teaches that current methods to prevent and treat GVDH involve administration of drugs such as cyclosporin-A and codicosteroids (column 1, lines 49-53).

It would have been obvious to one of ordinary skill in the art at the time of the invention to prevent or reduce the risk of developing graft-versus-host disease in a recipient of an organ or tissue transplant, comprising administering to the transplant recipient an adenosine deaminase inhibitor in a pharmaceutically effective amount within a predetermined time window before the transplantation as both Waller and Trotta teaches prevention of GVHD comprising administering an adenosine deaminase inhibitor (fludarabine and pentostatin, respectively). Motivation for the use of pentostatin for preventing GVHD in a patient who is a recipient of an organ or tissue transplant is provided by Trotta which teaches that infusion of a low concentration of DCF is specifically toxic to both B- and T-lymphocytes but does not impair the capacity of bone marrow stem cells to repopulate the hematopoietic system of lethally irradiated mice; these results may be directly applicable to the elimination of graft-versus-host reaction in humans as well as to the achievement of immunosuppression without toxicity to bone marrow and other proliferating cells (page 2189, column 2, last paragraph). It

would have also been obvious to one of ordinary skill in the art to prevent GVHD comprising the co-administration of pentostatin and cyclosporin-A as the use of materials in combination, each of which is known to function for intended purpose, is prima facie obvious. In the instant case, both pentostatin and cyclosporin-A are taught in the art as being useful for the prevention of GVHD. The formulation of a pharmaceutical composition into a form suitable for oral administration is seen as well within the purview of one of ordinary skill in the art at the time of the invention.

Conclusion

9. Claims 45-54 and 56 are pending. Claims 45-54 and 56 are rejected. No claims are allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Contacts

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick T. Lewis whose telephone number is 571-272-0655. The examiner can normally be reached on Monday - Friday between 10 am - 2 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Examiner
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